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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/932,521	08/17/2001	Hans Herweijer	Mirus.023.01	4294

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Mark K. Johnson
PO Box 510644
New Berlin, WI 53151-0644

EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/932,521	HERWEIJER ET AL.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *December 22, 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 11, 2003 has been entered.

DETAILED ACTION

This application claims benefit to provisional application 60/225,946 filed August 17, 2000.

Applicants' amendment filed December 22, 2003 has bee received and entered. Claims 1 and 18 have been amended. Claims 1-20 are pending and currently under examination.

Information Disclosure Statement

The Zhou et al. references J. Mol. Biol, 1997 has been received and entered. By providing the missing reference the request complies with 37 CFR 1.98(a)(2). The reference as listed in a previous IDS has been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to

> which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn.

Claims 1-20 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn.

Amendments to the claims have obviated the basis of the rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Initially, it is noted the amendments to the claims has obviated the basis of each of the specific rejections of record set forth in the previous office action.

Newly amended claims 1 and 18 are vague and unclear in the recitation of wherein expression of the transgene persists "for an extended period of time" because how long such period would be and how such a measurement would be made is not clearly set forth. The metes and bounds of the claim are unclear because the term "extended" is a subjective period of time

that would vary from one individual to another. Further, there is nothing in the claims that provide any characteristics of the vector, its delivery and the resulting period of time one would expect expression to occur for any particular vector. For example, it is unclear if a non-viral, linear DNA vector were delivered and expression was detected for 1 hour, one day or one week if each or any of these times would meet the limitations of the claims. As indicated in the previous office action, neither the claim nor the specification provides a clear nexus between step (a) delivering and step (b) expressing that results in the functional limitation of an "extended" period of time. Again, it appears that simply inserting a linear DNA vector into a mammal would and should inherently result in step (b), however the specification does not specifically support this analysis. Further, what an extended period of time for any vector encompassed by the claim is not clear. For example, comparing two given two vectors with two different promoters, the expression for one vector may be longer or more extended than the other, however each may be considered a long period of time for expression based on the amount of time measured. Moreover, the differences in expression are due to in part the promoters used and potentially in what cell the expression is measured.

Additionally, changes affected by the time at which this embodiment of expression is measured make the claim indefinite. For example, once the nucleic acid is delivered, one would not expect any significant amount of expression from either linear or circular sequences, however at a later time a difference may (or may not) be observed, and subsequently at an even later time expression in neither case will be detectable. Further, the claim is indefinite because the only means to know if one were infringing the claim would be to provide the relative comparison when the method is being practiced for each polynucleotide comprised by the

claims. Even given the examples and description in the specification of what an 'extended period of time' would be considered, whether this teaching is met, i.e. longer than 7 days or higher that 20%, would have to be specifically compared for each linear and each non-linear vector to see if the limitation is met. The claims are indefinite because the link between step (a) and (b) only fully can be determined upon a comparison, and is not subject to any simple guidance for only practicing step (a) alone. Dependent claims are included in the basis of the rejection because they only set forth structural features of the nucleic acid used in the method without indicating how they influence expression levels or how they may or may not affect the time of expression.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4, 7, 18 and 19 rejected under 35 U.S.C. 102(b) as being anticipated by Wolff *et al.* (Science, 1990) is withdrawn.

Claims 1, 2, 5, 7-13, 18 and 19 rejected under 35 U.S.C. 102(a) as being anticipated by Goryshin *et al.* (Nature Biotech, 2000) as evidenced by Gibco BRL (page 14-19) is withdrawn.

Claims 1, 2, 5, 7-13, 18 and 19 rejected under 35 U.S.C. 102(b) as being anticipated by Tucker *et al.* (US Patent 5,102,797, issued 1992) as evidenced by Gibco BRL (page 14-19) is withdrawn.

Amendments to the claims include embodiments not taught in the cited references, therefore obviate the basis of the rejection based on anticipation.

Claims 1, 16, 17 and 18 stand rejected under 35 U.S.C. 102(b) as being anticipated by Rolland *et al.* (US Patent 6,514,947).

Applicants note the amendments to the claims and argue that while Rolland *et al.* teach methods for the delivery of many forms of polynucleotides to mammals, including DNA as encompassed by the instant claims, Rolland *et al.* fail to teach that delivery of DNA would result in the extended transgene expression demonstrated in the instant specification. See middle of page 7 of Applicants' amendment. Applicants' arguments have been fully considered, but not found persuasive.

Initially, it is not clear if the results presented in the instant specification are consistent with only the working example (a specific cut plasmid) or if they extend to any linear polynucleotide as originally claimed (See *In re Dill*, 604 F.2d 1356, 1361, 202 USPQ 805, 808 (CCPA 1979) ("The evidence presented to rebut a *prima facie* case of obviousness must be commensurate in scope with the claims to which it pertains."). However, to the extent that the specific results would apply generally to any DNA vector as claimed, it is maintained that the

method steps taught by Rolland *et al.* would anticipate the methods as instantly claimed. Anticipation of the instantly claimed method only requires the teaching of each of the specific steps of the method. The unexpected results relied upon by Applicants are not active method steps, rather they are an inherent consequence of practicing the method as claimed and as taught by Rolland *et al.* As acknowledged by Applicants Rolland *et al.* teach the formulation of all known polynucleotides, so with respect to Rolland *et al.* teaching away, Examiner can not find any negative teaching of why the artisan would not use the form of liner DNA. Rolland *et al.* provide for methods for the delivery of a polynucleotide that when expressed produces a protein to provide the basis of a vaccine in a mammal. It is acknowledged that Rolland *et al.* do not specifically compare the expression pattern of various polynucleotides, however they clearly provide the limitations to practice the method as claimed. The expression of any DNA in a cell is a property dependent on many factors including the amount delivered, the to which it is delivered, the promoters used, and the complexity of sequence expressed, however in total is an inherent property of any of the polynucleotides delivered.

As noted in the previous office action, where the claimed and prior art process are identical or substantially identical, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. Whether the rejection is based on "inherency" under 35 USC 102, or "*prima facie* obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw,* 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). In the instant case, because the teachings of

Rolland *et al.* meet the structural limitations for practicing the methods as claimed, one would consider any functional limitation resulting from this practice would inherently result in the functional limitation set forth in step (b). Further, given the general and limited guidance of the specification for the types of polynucleotides contemplated for use in the claimed methods, there is no teaching nor evidence that any particular sequence that is provided in a linear form would not inherently result in the specific expression levels recited and required by the instant claims. Therefore, even though Rolland *et al.* do not specifically teach the functional limitation set forth in the claims that Applicants argue distinguishes the claimed invention from that disclosed, simply delivering any linear polynucleotide sequence would inherently result in this functional limitation.

As stated in the previous office action, Rolland *et al.* teach a method for the delivery and expression of a nucleic acid vector to an mammal *in vivo* (see summary in abstract and claim 1 for example). More specifically, Rolland *et al.* teach that a nucleic acid vector can be many forms of non-viral nucleic acids including RNA, cDNA and plasmid DNA (column 2, lines 37-40). Furthermore, though it is known in the art that cDNA and RNA are linear nucleic acids, Rolland *et al.* specifically teach that whatever vector used can be provided in a linear form (column 2, lines 58-59). Rolland *et al.* teach that the vector can comprise one or more genes to be expressed (column 2, lines 58-59), and by way of example a reduction to practice using the expression and detection of the luciferase and CAT transgenes is provided (see figures 6 and 8, on sheet 5 of 8). Finally, Rolland *et al.* teach that various routes of delivery can be used including within the muscle or interstitial space of a joint (column 2, lines 30-33 and claims 5 and 8).

Thus, the teaching of Rolland *et al.* for the delivery of linear nucleic acid sequences and expression of said sequences *in vivo* anticipates the instantly claimed invention.

Claims 1, 5, 7, 18 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Nabel *et al.* (US Patent 5,733,543 issued March 31, 1998).

Nabel *et al.* teach a method of stably introducing transgenes into mammalian cells. In exploring the efficiency of their invention, Nabel *et al.* use a plasmid construct that will express REV M10 that was linearized with a restriction enzyme. See specification starting at column 21, line 64 to column 22, line 30, including Table 1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 6, 18 and 20 rejected under 35 U.S.C. 103(a) as being unpatentable over Tucker *et al.* (US Patent 5,102,797) in view of Sambrook et al. (Molecular Cloning, Vol 2, section 14.5, 1989) is withdrawn

Amendments to the claims have differentiated the claimed invention from that taught in Tucker *et al.* (US Patent 5,102,797) in view of Sambrook *et al.*

Claims 1, 7, 14, 15, 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rolland *et al.* (US Patent 6,514,947) or Nabel *et al.* (US Patent 5,733,543) in view of Budker *et al.* (Gene Therapy, 5:272-276, 1998).

Applicants argue that the claims as amended have obviated the basis of the rejection as reasoned above for the rejection made under 25 USC 102. See Applicants' amendment, page 8. Applicants' arguments have been fully considered, but not found persuasive.

As note above, Applicants are relying on previously uncharacterized affects of delivering a linear DNA to a cell in order to differentiate the instantly claimed method from that taught in Rolland *et al.* These arguments are not found persuasive because the inherent property relied upon is not an active step in the claimed method. Moreover, based on the many factors affecting the expression of a vector, it is not clear if the working example truly represents an unexpected result that can be extended to any polynucleotide. Even accepting the arguments as true, they do not establish that the claimed method steps are not unobvious over the prior art. All the record currently affirms is that the specific conditions used in the working example provide a different expression pattern. The reason for the difference in the expression pattern and the ability to extend the difference to other sequences is not clearly set forth, and is found insufficient to

obviate the basis of obviousness rejection. (*In re D'Ancicco, Collins, and Shine*, 169 USPQ 303 (CCPA 1971) and *In re Papesch*, 50 CCPA 1084, 315 F.2d 381, 137 USPQ 43 (1963)).

As stated in the previous office action, the structural limitations of the claims, *i.e.* generated by PCR or generated from a plasmid and delivered by various routes are taught by the cited references. Again, it is noted that Applicants do not argue that providing any particular linear nucleic acid sequence would provide an unexpected result over that disclosed in the prior art, rather it is argued that the particular functional limitations recited in the claims for providing a linear nucleic acid sequence are not specifically taught. As explained above, because the functional limitation of practicing the method set forth in Rolland *et al.* anticipate the method as claimed, and lacking evidence to the contrary, practice of the method with the delivery of any linear polynucleotide would result in the functional limitation recited in the amended claims. As set forth previously and above, Rolland *et al.* teach that a nucleic acid vector can be many forms of non-viral nucleic acids including plasmid DNA (column 2, lines 37-40). Rolland *et al.* teach that the vector can comprise one or more genes to be expressed (column 2, lines 58-59), and by way of example a reduction to practice using the expression and detection of the luciferase and CAT transgenes is provided (see figures 6 and 8, on sheet 5 of 8). Finally, Rolland *et al.* teach that various routes of delivery can be used highlighting several routes known and used in the art (column 2, lines 30-33).

Nable e*t al.* is summarized above and provides similar teaching to that disclosed in Rolland et al. Nable e*t al.* provide several working examples where linear non-viral DNA is delivered and expressed.

Thus, the claimed invention of delivering a non-viral nucleic acid to cell *in vivo* made by PCR by intravascular injection as a whole was clearly *prima facie* obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (571) 272-0734.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

Joseph T. Woitach

Joe Woitach
AU1632